WEST

Generate Collection

L8: Entry 1 of 23 File: USPT May 1, 2001

DOCUMENT-IDENTIFIER: US 6224883 B1
TITLE: Process and composition for therapeutic cisplatin (CDDP)

BSPR:
Sternlicht et al. (1989) Radiology 170:1073-1075 investigates renal cisplatin chemoembolization with angiostat, gelfoam, and ethiodol. A combination chemoembolization therapy for hepatocellular carinoma is described in Yodono et al. (1989) Cancer Chem. and Pharm. 23:S42-S44. The reduction of systemic exposure and toxicity of cisplatin by encapsulation in poly-lactide-co-glycolide is taught by Verrijk et al. (1992) Cancer Res. 52:6653-6656.

ORPL:
Verrijk et al., "Reduction of Systemic Exposure and Toxicity of Cisplatin by Encapsulation in Polylactide-co-glycolide," Cancer Research, 52:6653-6656 (1992).

WEST

Generate Collection

L8: Entry 2 of 23 File: USPT Oct 3, 2000

DOCUMENT-IDENTIFIER: US 6126966 A
TITLE: Liposomes containing a cisplatin compound

DEPR:
In the example detailed below, the vesicle-forming lipid HSPC, the derivatized vesicle-forming lipid PEG-DSPE and cholesterol are dissolved in ethanol heated to about 65.degree. C., just above HSPC phase transition temperature's between about 52-60.degree. C. An aqueous solution of native cisplatin is heated to between 63-67.degree. C. The solutions are mixed together to form liposomes containing the cisplatin compound in entrapped form. The method of the invention achieves a high encapsulation of cisplatin, typically encapsulating between 10-20 .mu.g drug/mg lipid, and provides liposomes having, in addition to the outer surface coating, an inner surface coating of hydrophilic polymer chains, with the cisplatin compound stably entrapped within the liposome.

DEPR:
The final liposomes contained an internal phase of cisplatin encapsulated at a concentration of 8.5 mg/ml in 0.9% sodium chloride and an external phase of sucrose/sodium chloride solution. Prior to packaging for stability studies, described below, and/or prior to administration, the liposome suspension was brought to a cisplatin concentration of 1.05 mg/ml with a sucrose/sodium chloride/histidine solution and the pH was adjusted to 6.5.

DEPR:
The stability of liposomes prepared as described above (Example 3) was evaluated by (i) analyzing the liposomal suspension for cisplatin and platinum concentrations, (ii) determining percent of encapsulated platinum, (iii) measuring liposome size, and (iv) measuring the pH of the liposome suspension, each as a function of time and temperature.

DEPR:
Under more aggressive storage conditions of 30.degree. C. and 40.degree. C., some decrease in cisplatin and platinum concentrations was observed, and the percentage of encapsulated platinum was 93% after 3 months at 30.degree. C. and 91% after 1 month at 40.degree. C. Little change in liposome size was observed.

DEPR:
The data indicates that the liposome composition of the present invention is effective to retain the cisplatin in the liposomes in its native form, thereby providing a stable liposome composition. This stability is evidenced in particular by the 18 month time point at 2-8.degree. C., where the concentration of cisplatin remained constant and 99% of the platinum was encapsulated in the liposomes.

DEPR:
In a first study (Example 5A), the liposome compositions were incubated at 60.degree. C. for 6 hours. After incubation, the cisplatin concentration of the liposomal suspension, the percentage of encapsulated platinum, liposome size and suspension pH were measured, according to the procedures described above. The results, summarized in Table 2, show that after the incubation period, the liposome composition of the present invention had a 24% (0.38 mg/ml to 0.29 mg/ml) decrease in cisplatin concentration, whereas the cisplatin concentration of the comparative liposomal suspension decreased by 44% (0.25 mg/ml to 0.14 mg/ml). The percentage of

DEPR:

It is clear from the data shown in Table 4 that compared to liposomes lacking an inner and outer surface coating of hydrophilic polymer chains, the liposome composition of the present invention having such a surface coating is effective to reduced the loss of cisplatin from the liposomes. In particular, the liposome composition is effective to reduce conversion of cisplatin to other molecular species, as evidenced by comparing the cisplatin concentrations and the percentage of encapsulated platinum for the two compositions.

DEPR:
The warm lipid solution was rapidly added to the warm (63-67.degree. C.) drug solution, with mixing, to form a suspension of liposomes having heterogeneous sizes. The suspension was mixed for one hour at 63-67.degree. C. The cisplatin concentration in the hydration mixture was 7.2 mg/ml and, at this stage, approximately 30% of the drug was encapsulated in the liposomes. 10% of the total solution volume was ethanol and the total lipid concentration was 150 mg lipid/ml.

DEPR:
Stability of the comparative liposome composition and the liposome composition of the present invention were compared by diluting the liposome samples with saline (1:1 v:v) and incubating the suspensions for 6 hours at 60.degree. C. After incubation, the samples were tested for cisplatin concentration, % platinum encapsulation, liposome size and pH, according to the procedures described in Example 4. The results are summarized in Table 2.

DEPR:
The liposome compositions were diluted to a cisplatin concentration of 1 mg/ml with the histidine/sucrose/sodium chloride diluent described in Example 3G. The liposome suspensions were incubated at 40.degree. C. for 2 weeks, after which the cisplatin concentration, % platinum encapsulation, liposome size and pH were measured. The results are summarized in Table 3.

DEPV:
3. Percent of encapsulated platinum: The percent encapsulated platinum was determined by separating the liposomes from unencapsulated cisplatin by size-exclusion chromatography and assaying the liposomal and drug fractions for platinum content by atomic absorption;

ORPL:
Freise, W.H. et al., "Pharmacokinetics of Liposome Encapsulated Cisplatin in Rats," Arch. Int. Pharmacodyn. 258: 180-192 (1982).

ORPL:
Gondal, J.A. et al., "Comparative Pharmacological, Toxicological and Antitumoral Evaluation of Free and Lipsome-Encapsulated Cisplatin in Rodents," Eur J Cancer. 29A:(11) 1536-1542 (1993).

ORPL:
Potkul, R.K. et al., "Toxicities in Rats with Free Versus Liposomal Encapsulated Cisplatin," Am J Obstet Gynecol. 164:(02) 652-658 (1991).

L5 ANSWER 1 OF 2 INPADOC COPYRIGHT 2001 EPO DUPLICATE 1

LEVEL 1
AN 150322471 INPADOC ED 20010605 EW 200122 UP 20010719 UW 200128
TI THERAPY FOR HUMAN CANCERS USING **CISPLATIN** AND OTHER DRUGS OR GENES ENCAPSULATED INTO LIPOSOMES
IN BOULIKAS, TENI
INS **BOULIKAS TENI**
INA US
PA BOULIKAS, TENI
PAS BOULIKAS TENI
PAA US
TL English; French
LA English
DT Patent
PIT WOA1 PUBL.OF THE INT.APPL. WITH INT.SEARCH REPORT
PI WO 2001034130 A1 20010517
DS RW: GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AI WO 2000-US29723 A 20001027
PRAI US 1999-434345 A 19991105
OSCA 134:371773
AB A method for encapsulating **cisplatin** and other positively-charged drugs into liposomes having a different lipid composition between their inner and outer membrane bilayers is disclosed.
The liposomes are able to reach primary tumors and their metastases after intravenous injection to animals and humans. The encapsulated **cisplatin** has a high therapeutic efficacy in eradicating a variety of solid human tumors including but not limited to breast carcinoma and prostate carcinoma. Combination of the encapsulated **cisplatin** with encapsulated doxorubicin or with other antineoplastic drugs are claimed to be of therapeutic value. Also of therapeutic value in cancer eradication are claimed to be combinations of encapsulated **cisplatin** with a number of anticancer genes including but not limited to p53, IL-2, IL-12, angiostatin, and oncostatin encapsulated into liposomes as well as combinations of encapsulated **cisplatin** with HSV-tk plus encapsulated ganciclovir.

L5 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
AN 96200711 MEDLINE
DN 96200711 PubMed ID: 8615613
TI DNA lesion-recognizing proteins and the p53 connection.
AU **Boulikas T**
CS Institute of Molecular Medical Sciences, Palo Alto, California 94306, USA.
SO ANTICANCER RESEARCH, (1996 Jan-Feb) 16 (1) 225-42. Ref: 187
Journal code: 59L; 8102988. ISSN: 0250-7005.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
E

L12 ANSWER 27 OF 29 CAPLUS COPYRIGHT 2001 ACS
AN 1989:412523 CAPLUS
DN 111:12523
TI Pharmaceutical liposomes containing phospholipids and anionic surfactants
IN Hamaguchi, Naoru; Iga, Katsumi; Ogawa, Yasuaki
PA Takeda Chemical Industries, Ltd., Japan
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 280492	A2	19880831	EP 1988-301486	19880222
	EP 280492	A3	19891004		
	EP 280492	B1	19920122		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	DK 8800869	A	19880826	DK 1988-869	19880219
	JP 64000014	A2	19890105	JP 1988-39129	19880222
	JP 2611307	B2	19970521		
	AT 71834	E	19920215	AT 1988-301486	19880222
	HU 52943	A2	19900928	HU 1988-892	19880224
	HU 203278	B	19910729		
	US 5019394	A	19910528	US 1988-159945	19880224
	CA 1322171	A1	19930914	CA 1988-559633	19880224
	CN 88100965	A	19880907	CN 1988-100965	19880225
	CA 1335349	A1	19950425	CA 1989-598491	19890502
PRAI	JP 1987-43442		19870225		
	EP 1988-301486		19880222		

OS MARPAT 111:12523
AB Liposomes comprise an active agent, a membrane consisting of phospholipids
contg. satd. acyl groups and an anionic surfactant with a Krafft point .gtoreq.37.degree.. A mixt. of 270 mg dipalmitoylphosphatidylcholine and 30 mg distearoylphosphatidylcholine in 70 mL 1:1 CHCl3/iso-Pr2O was added to 10 mL aq. soln. contg. 6-carboxyfluorescein and 30 mg Na stearoylmethyltaurine at room temp. The latter was almost insol. in this mixt. but dissolved rapidly forming **micelles** at temps. above the Krafft point. The above mixt. was sonicated and the org. solvent was removed to give reverse-phase-evapn. vesicles. The entrapment ratio of 6-carboxyfluorescein was 33.2%. The blood level of the above liposome compn. was 9.7 times higher 1 h after i.v. administration than that obtained by administration of control liposomes without surfactants. Liposomes prepd. from egg yolk phosphatidylcholines, cholesterol, and surfactants were eliminated as rapidly as the control liposomes. The above described procedure was followed to prep. a formulation contg. 500 .mu.g/mL **Cisplatin** and 30 mg Na stearoylmethyltaurine. The liposome/**Cisplatin** entrapment ratio was 21.4%.

L12 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2001 ACS
AN 1990:16254 CAPLUS
DN 112:16254
TI Targeted delivery of drugs and diagnostic agents using carriers which promote endothelial and epithelial uptake and lesional localization
IN Ranney, David F.
PA USA
SO PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8807365	A2	19881006	WO 1988-US1096	19880330
	WO 8807365	A3	19881117		
	W: AT, AU, BB, BG, BR, CH, DE, DK, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU, US				
	RW: AT, BE, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 4925678	A	19900515	US 1987-33432	19870401
	AU 8816275	A1	19881102	AU 1988-16275	19880330
	AU 607494	B2	19910307		
	EP 352295	A1	19900131	EP 1988-903702	19880330
	EP 352295	B1	19930616		
	EP 352295	B2	19960410		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	JP 04504404	T2	19920806	JP 1988-503579	19880330
	JP 2886171	B2	19990426		
	AT 90554	E	19930715	AT 1988-903702	19880330
	CA 1324080	A1	19931109	CA 1988-565119	19880426
	US 5108759	A	19920428	US 1989-448121	19891208
PRAI	US 1987-33432		19870401		
	EP 1988-903702		19880330		
	WO 1988-US1096		19880330		

AB Targeted delivery systems comprise drugs or diagnostic agents and carriers which recognize determinants present on normal or diseased endothelium. This induces the following effects in vivo: (1) rapid endothelial envelopment of the carrier; (2) sequestration of the carrier and protection of the entrapped agent from early blood clearance; (3) acceleration of the carrier's transport across the vascular endothelium into the interstitium; and (4) improvement of drug delivery across the endothelium, so that a lower total drug dose is required. Aq. **cisplatin** (I) was mixed with heparin at a 1:1.1 wt. ratio and ultrasonicated to form a heparin-coated I microemulsion with particle sizes of 0.2-1.5 .mu.m, which was stable for >1 h at 22.degree.. Mice receiving this emulsion i.v. showed moderate to intense concn. of I in the lung interstitia, alveolar pneumocytes, respiratory epithelia, and lymph nodes, but low I concns. in the liver, whereas mice receiving std. aq. I showed intense I concn. in the liver and almost no I in the lungs. Thus high concns. of I (which are usually toxic to endothelium) can be successfully reformulated as a heparin microemulsion, and the heparin component can induce endothelial binding and transcellular uptake of the complexes in a fashion that protects the endothelium from the toxic effects of the drug.

L12 ANSWER 24 OF 29 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95309413 EMBASE
DN 1995309413
TI Block copolymer **micelles** as long-circulating drug vehicles.
AU Kwon G.S.; Kataoka K.
CS Dept. Material Science/Technology, Research Institute for Biosciences, Science University of Tokyo, Yamazaki 2641,Noda-shi, Chiba 278, Japan
SO Advanced Drug Delivery Reviews, (1995) 16/2-3 (295-309).
ISSN: 0169-409X CODEN: ADDREP
CY Netherlands
DT Journal; General Review
FS 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The development of block copolymer **micelles** as long-circulating drug vehicles is described. As well, a recent fundamental study of block copolymer **micelles**, where much insight into their structures and properties has been realized, is briefly summarized in order to shed light on their properties in vivo. There is emphasis on block copolymer **micelles** having poly(ethylene oxide) as the hydrophilic block and poly(L-amino acid) as the hydrophobic block, with some discussion on the properties of poly(ethylene oxide). Comparisons are drawn with other drug vehicles and with **micelles** formed from low molecular weight surfactants. **Micelle**-forming, block copolymer-drug conjugates are described. Hydrophobic drugs, such as doxorubicin, distribute into block copolymer **micelles**, and details of several examples are given. Finally, the paper presents studies that evidence the long circulation times of block copolymer **micelles**. Like long-circulating liposomes, block copolymers that form **micelles** accumulate passively at solid tumors and thus have great potential for anti-cancer drug delivery.

L12 ANSWER 21 OF 29 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
AN 96198216 EMBASE
DN 1996198216
TI Introduction of **cisplatin** into polymeric **micelle**.
AU Yokoyama M.; Okano T.; Sakurai Y.; Suwa S.; Kataoka K.
CS Institute of Biomedical Engineering, Tokyo Women's Medical College, Kawada-cho,Shinjuku-ku, Tokyo 162, Japan
SO Journal of Controlled Release, (1996) 39/2-3 (351-356).
ISSN: 0168-3659 CODEN: JCREEC
CY Netherlands
DT Journal; Conference Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB **Cisplatin**, an anticancer drug, was bound to aspartic acid residues of poly(ethylene glycol)-poly(aspartic acid) block copolymer (PEG-P(Asp)) by ligand substitution reaction at platinum atoms of **cisplatin**. At a molar ratio of **cisplatin** and the aspartic acid residue of 1:1, polymeric **micelles** were formed with an average diameter of 16 nm. A polymeric **micelle** fraction was easily purified by ultrafiltration, and a micellar structure of this fraction was stable in distilled water and NaCl solution at 37.degree.C for 24 h. The polymeric **micelle** showed 1/8 to 1/5 cytotoxicity of intact **cisplatin** against murine B 16 melanoma cells during 24-72 h incubation. This suggests release of platinum complexes from the

L12 ANSWER 14 OF 29 CAPLUS COPYRIGHT 2001 ACS
AN 1998:548519 CAPLUS
DN 129:193714
TI Liposomes containing active agents
IN Needham, David; Sarpal, Ranjit S.
PA Duke University, USA
SO PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9834597	A1	19980813	WO 1998-US2154	19980205
	W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5827533	A	19981027	US 1997-795100	19970206
	AU 9863196	A1	19980826	AU 1998-63196	19980205
	US 5882679	A	19990316	US 1998-129654	19980805
	US 6143321	A	20001107	US 1998-174775	19981019
PRAI	US 1997-795100	A1	19970206		
	US 1998-17984	A3	19980203		
	WO 1998-US2154	W	19980205		

AB Liposomes formulations for i.v. administration contg. a poorly water-sol. active agent in the lipid bilayer of the liposome and/or entrapped in **micelles** within the liposome interior space are designed to maximize the amt. of active agent that can be carried by the liposomes. The bilayer membrane comprises a vesicle-forming lipid and an amt. of hydrophilic polymer-derivatized vesicle-forming lipid and/or cholesterol sufficient to inhibit fusion of the liposome membrane with an active agent-lipid surfactant aggregate entrapped therein and thereby preserve the phys. integrity of the liposomes. The hydrophilic polymer is e.g. PEG, poly(lactic acid), poly(glycolic acid), lactic acid/glycolic acid copolymer, or poly(vinyl alc.). For the lipid bilayer to be stable in the presence of **micelles**, the **micelle**-forming surfactant must have a low crit. **micelle** concn.; a suitable surfactant is monooleoylphosphatidylcholine (MOPC; crit. **micelle** concn. .apprx.3 .mu.M). Thus, taxol was solubilized by incorporation into MOPC **micelles** in a 1:5 molar ratio. Liposomes produced at a 1-stearoyl-2-oleoyl-sn-glycero-3-phosphocholine (SOPC)/MOPC mol ratio of 16:4, contained .ltoreq.1.7 mM taxol after extrusion and cleaning, compared to 0.5 mM for SOPC liposomes in the absence of MOPC. Incorporation of cholesterol stabilized the liposome bilayer; the optimal SOPC/cholesterol ratio was 2:1.

L12 ANSWER 15 OF 29 CAPLUS COPYRIGHT 2001 ACS
AN 1998:394198 CAPLUS
DN 129:62955
TI Antitumor cisplatinum prodrugs
IN De Kruijff, Ben; Speelmans, Gelske; Staffhorst, Rutger Willibrordus

Hendricus Maria; Reedijk, Jan

PA Rijksuniversiteit Utrecht, Neth.; Seed Capital Investments-2 B.V.; De Kruijff, Ben; Speelman, Gelske; Staffhorst, Rutger Wilbrordus Hendricus Maria; Reedijk, Jan

SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9824424	A1	19980611	WO 1996-NL474	19961203
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9677110	A1	19980629	AU 1996-77110	19961203
	WO 9824425	A1	19980611	WO 1997-NL661	19971203
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9854168	A1	19980629	AU 1998-54168	19971203

PRA

L18 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
AN 1998153116 MEDLINE
DN 98153116 PubMed ID: 9485383
TI Membrane fusion induced by 11-mer anionic and cationic peptides: a structure-function study.
AU Pecheur E I; Martin I; Ruysschaert J M; Bienvenue A; Hoekstra D
CS Department of Physiological Chemistry, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.. e.pecheur-huet@med.rug.nl
SO BIOCHEMISTRY, (1998 Feb 24) 37 (8) 2361-71.
Journal code: A0G; 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199803
ED Entered STN: 19980407
Last Updated on STN: 19980407
Entered Medline: 19980320
AB We recently demonstrated that an amphipathic net-**negatively** charged peptide consisting of 11 **amino acids** (WAE 11) strongly promotes fusion of large unilamellar liposomes (LUV) when anchored to a liposomal membrane [Pecheur, E. I., Hoekstra, D., Sainte-Marie, J., Maurin, L., Bienvenue, A., and Philippot, J. R. (1997) Biochemistry 36, 3773-3781]. To elucidate a potential relationship between peptide structure and its fusogenic properties and to test the hypothesis that specific structural motifs are a prerequisite for WAE-induced fusion, three 11-mer WAE-peptide analogues (WAK, WAEPro, and WAS) were synthesized and investigated for their structure and fusion activity. Structural analysis of the synthetic peptides by infrared attenuated total reflection spectroscopy reveals a distinct propensity of each peptide toward a helical structure after their anchorage to a liposomal surface, emphasizing the importance of anchorage on conveying a secondary structure, thereby conferring fusogenicity to these peptides. However, whereas WAE and WAK peptides displayed an essentially nonleaky fusion process, WAS- and WAEPro-induced fusion was accompanied by substantial leakage. It appears that peptide helicity as such is not a sufficient condition to convey optimal fusion properties to these 11-mer peptides. Studies of changes in the intrinsic Trp fluorescence and iodide quenching experiments were carried out and revealed the absence of migration of the Trp residue of WAS and WAEPro to a hydrophobic environment, upon their interaction with the target membranes. These results do not support the penetration of both peptides as their mode of membrane interaction and destabilization but rather suggest their folding along the vesicle surface, posing them as surface-seeking helixes. This is in striking contrast to the behavior observed for WAE and WAK, for which at least partial penetration of the Trp residue was demonstrated. These results indicate that subtle differences in the primary sequence of a **fusogenic peptide** could induce dramatic changes in the way the peptide interacts with a bilayer, culminating in equally drastic changes in their functional properties. The data also reveal a certain degree of sequence specificity in WAE-induced fusion.

L23 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1991:192593 CAPLUS
DN 114:192593
TI Nonphospholipid pharmaceutical liposomes
IN Radhakrishnan, Ramachandran
PA Liposome Technology, Inc., USA
SO PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9006775	A1	19900628	WO 1989-US5525	19891206
	W: AU, DK, FI, JP, NO				
	RW: AT, BE, CH, DE, ES, FR, GB, IT, LU, NL, SE				
	US 4906476	A	19900306	US 1988-284158	19881214
	US 5043165	A	19910827	US 1988-284216	19881214
PRAI	US 1988-284158		19881214		
	US 1988-284216		19881214		

AB A nonconventional liposome compn. consisting of nonphospholipid lipids, esp. cholesterol and cholesterol ester salts, are used for **encapsulation** of drugs. They are useful for sustained release of steroids, and are suitable for treatment of inflammatory, arthritic, rheumatoid diseases, etc., esp. as aerosols for interstitial lung disease.

Beclomethasone dipropionate (I) 10 was incorporated into liposomes prepd. with Na cholesterol sulfate 50 and cholesterol 40 mol %. Sustained release of I was obsd. in rats following intratracheal administration, in contrast to liposomes formulated with phosphatidylcholine and cholesterol.

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=> d his

     (FILE 'HOME' ENTERED AT 18:18:14 ON 02 AUG 2001)

     FILE 'MEDLINE' ENTERED AT 18:18:21 ON 02 AUG 2001
L1             4 S CISPLATIN AND MICELLE#/AB,BI
L2             8 S MICELLE# AND FUSOGENIC/AB,BI

     FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS' ENTERED AT 18:22:34 ON
02
     AUG 2001
                 E BOULIKAS T/AU
L3           212 S E3-E4
L4             6 S L3 AND CISPLATIN/AB,BI
L5             2 DUP REM L4 (4 DUPLICATES REMOVED)
L6             1 S L3 AND MICELLE#/AB,BI
L7            40 S CISPLATIN AND MICELLE#/AB,BI
L8             2 S L7 AND ETHANOL/AB,BI
L9             2 DUP REM L8 (0 DUPLICATES REMOVED)
L10            5 S MICELLE# AND FUSOGENIC PEPTIDE#/AB,BI
L11            2 DUP REM L10 (3 DUPLICATES REMOVED)
L12           29 DUP REM L7 (11 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 18:28:21 ON 02 AUG 2001

     FILE 'MEDLINE' ENTERED AT 18:34:40 ON 02 AUG 2001
L13            0 S AQUAPLATIN/AB,BI

     FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS' ENTERED AT 18:35:22 ON
02
     AUG 2001
L14            0 S L13
L15            0 S FUSOGENIC PEPTIDE AND DERIVATIZED/AB,BI
L16           17 S FUSOGENIC PEPTIDE AND NEGATIVE?/AB,BI
L17            6 S L16 AND AMINO ACIDS/AB,BI
L18            2 DUP REM L17 (4 DUPLICATES REMOVED)
L19            0 S AQUAPLATIN/AB,BI

     FILE 'BIOBUSINESS' ENTERED AT 18:38:47 ON 02 AUG 2001
L20            0 S L19

     FILE 'MEDLINE' ENTERED AT 18:39:11 ON 02 AUG 2001

     FILE 'MEDLINE, EMBASE, BIOSIS, INPADOC, CAPLUS' ENTERED AT 18:40:17 ON
02
     AUG 2001
L21            0 S CISPLATIN MICELLE#/AB,BI
L22            2 S CISPLATIN AND MICELLE# AND ENCAPSULAT?/AB,BI
L23            2 DUP REM L22 (0 DUPLICATES REMOVED)
L24            0 S FUSOGENIC PEPTIDE AND LIPID CONJUGATE/AB,BI
L25          220 S FUSOGENIC PEPTIDE# OR FUSOGENIC POLYPEPTIDE#/AB,BI
L26            5 S L25 AND DOPE/AB,BI
L27            3 DUP REM L26 (2 DUPLICATES REMOVED)
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L27 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:247845 BIOSIS
DN PREV199900247845
TI Gene delivery mediated by cationic liposomes: From biophysical aspects to enhancement of transfection.
AU Pedroso de Lima, Maria C. (1); Simoes, Sergio; Pires, Pedro; Gaspar, Rogerio; Slepushkin, Vladimir; Duzgunes, Nejat
CS (1) Department of Biochemistry, Faculty of Science and Technology, University of Coimbra, Coimbra Portugal
SO Molecular Membrane Biology, (Jan.-March, 1998) Vol. 16, No. 1, pp. 103-109.
ISSN: 0968-7688.
DT Article
LA English
SL English
AB Cationic liposomes complexed with DNA have been used extensively as non-viral vectors for the intracellular delivery of reporter or therapeutic genes in culture and in vivo. However, the relationship between the features of the lipid-DNA complexes ('lipoplexes') and their mode of interaction with cells, the efficiency of gene transfer and gene expression remain to be clarified. To gain insights into these aspects, the size and zeta potential of cationic liposomes (composed of 1,2-dioleoyl-3-(trimethylammonium) propane (DOTAP) and its mixture with phosphatidylethanolamine (PE)), and their complexes with DNA at different (+/-) charge ratios were determined. A lipid mixing assay was used to assess the interaction of liposomes and lipoplexes with monocytic leukaemia cells. The use of inhibitors of endocytosis indicated that fusion of the cationic liposomes with cells occurred mainly at the plasma membrane level. However, very limited transfection of these cells was achieved using the above complexes. It is possible that the topology of the cationic liposome-DNA complexes does not allow the entry of DNA into cells through a fusion process at the plasma membrane. In an attempt to enhance transfection mediated by lipoplexes composed of DOTAP and its equimolar mixture with dioleoylpho-sphatidylethanolamine (**DOPE**) two different strategies were explored: (i) association of a targeting ligand (transferrin) to the complexes to promote their internalization, presumably by receptor-mediated endocytosis; and (ii) association of synthetic **fusogenic peptides** (GALA or the influenza haemagglutinin N-terminal peptide HA-2) to the complexes to promote endosomal destabilization and release of the genetic material into the cytoplasm. These strategies were effective in enhancing transfection in a large variety of cells, including epithelial and lymphoid cell lines, as well as human macrophages, especially with the use of optimized lipid/DNA (+/-) charge ratios. Besides leading to high levels of transfection, the ternary complexes of cationic liposomes, DNA, and protein or peptide, have the advantages of being active in the presence of serum and being non-toxic. Moreover, such ternary complexes present a net negative charge and, thus, are likely to alleviate the problems associated with the use of highly positively charged complexes in vivo, such as avid complexation with serum proteins. Overall, the results indicate that these complexes, and their future derivatives, may constitute viable alternatives to viral vectors for gene delivery in vivo.

L27 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS
AN 1997:463772 CAPLUS
DN 127:126437
TI Enhancement of cationic liposome-mediated gene delivery by transferrin and **fusogenic peptides**
AU Simoes, S.; Slepushkin, V.; Gaspar, R.; De Lima, M.C. Pedroso; Duzgunes, N.
CS Department of Microbiology, University of the Pacific, San Francisco, CA, 94115, USA
SO Proc. Int. Symp. Controlled Release Bioact. Mater. (1997), 24th, 659-660
CODEN: PCRMEY; ISSN: 1022-0178
PB Controlled Release Society, Inc.
DT Journal
LA English
AB The use of transferrin to promote internalization of lipid-DNA complexes possible via receptor-ligand mediated endocytosis results in a considerable enhancement of transfection mediated by DOTAP:**DOPE** (1:1) liposomes. Assocn. of **fusogenic peptides** with the lipid-DNA complexes enhances the level of gene expression.